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Young, Jim ; Xiao, Yongling ; Moodie, Erica E M ; Abrahamowicz, Michal ; Klein, Marina B ; Bernasconi, Enos ; Schmid, Patrick ; Calmy, Alexandra ; Cavassini, Matthias ; Cusini, Alexia ; Weber, Rainer ; Bucher, Heiner C

Abstract: **BACKGROUND:** Patients with HIV exposed to the antiretroviral drug abacavir may have an increased risk of cardiovascular disease (CVD). There is concern that this association arises because of a channeling bias. Even if exposure is a risk, it is not clear how that risk changes as exposure cumulates. **METHODS:** We assess the effect of exposure to abacavir on the risk of CVD events in the Swiss HIV Cohort Study. We use a new marginal structural Cox model to estimate the effect of abacavir as a flexible function of past exposures while accounting for risk factors that potentially lie on a causal pathway between exposure to abacavir and CVD. **RESULTS:** A total of 11,856 patients were followed for a median of 6.6 years; 365 patients had a CVD event (4.6 events per 1000 patient-years). In a conventional Cox model, recent-but not cumulative-exposure to abacavir increased the risk of a CVD event. In the new marginal structural Cox model, continued exposure to abacavir during the past 4 years increased the risk of a CVD event (hazard ratio = 2.06; 95% confidence interval: 1.43 to 2.98). The estimated function for the effect of past exposures suggests that exposure during the past 6-36 months caused the greatest increase in risk. **CONCLUSIONS:** Abacavir increases the risk of a CVD event: the effect of exposure is not immediate, rather the risk increases as exposure cumulates over the past few years. This gradual increase in risk is not consistent with a rapidly acting mechanism, such as acute inflammation.

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Effect of Cumulating Exposure to Abacavir on the Risk of Cardiovascular Disease Events in Patients From the Swiss HIV Cohort Study

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Background: Patients with HIV exposed to the antiretroviral drug abacavir may have an increased risk of cardiovascular disease (CVD). There is concern that this association arises because of a channeling bias. Even if exposure is a risk, it is not clear how that risk changes as exposure cumulates.

Methods: We assess the effect of exposure to abacavir on the risk of CVD events in the Swiss HIV Cohort Study. We use a new marginal structural Cox model to estimate the effect of abacavir as a flexible function of past exposures while accounting for risk factors that potentially lie on a causal pathway between exposure to abacavir and CVD.

Results: A total of 11,856 patients were followed for a median of 6.6 years; 365 patients had a CVD event (4.6 events per 1000 patient-years). In a conventional Cox model, recent—but not cumulative—exposure to abacavir increased the risk of a CVD event. In the new marginal structural Cox model, continued exposure to abacavir during the past 4 years increased the risk of a CVD event (hazard ratio = 2.06;

95% confidence interval: 1.43 to 2.98). The estimated function for the effect of past exposures suggests that exposure during the past 6–36 months caused the greatest increase in risk.

Conclusions: Abacavir increases the risk of a CVD event: the effect of exposure is not immediate, rather the risk increases as exposure cumulates over the past few years. This gradual increase in risk is not consistent with a rapidly acting mechanism, such as acute inflammation.

Key Words: HIV, antiretroviral therapy, reverse transcriptase inhibitors, adverse effects, marginal structural models

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INTRODUCTION

In 2008, an analysis by the D:A:D collaboration of observational cohorts showed that recent exposure to the antiretroviral drug abacavir was associated with an increased

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risk of cardiovascular disease (CVD) events.¹ Subsequent meta-analyses of randomized controlled trials failed to find evidence of this association.^{2–5} The D:A:D emphasized that stopping smoking would do more to reduce the risk of a heart attack than stopping abacavir and noted that the absolute risk of such events was low.⁶ Nevertheless, their results caused an unprecedented change in prescribing behavior.⁷

Neither cumulative nor past exposure to abacavir seemed to increase the risk of these events,¹ and the D:A:D collaboration observed that while current use was a risk, this risk seemed to reverse shortly after the use of abacavir ceased.⁸ These factors led the collaboration to suggest that a rapidly acting mechanism, such as vascular inflammation, could be responsible for the increase in risk. However, subsequent biomarker studies proved inconclusive^{9–12} and analyses of other observational cohorts led to inconsistent results.^{9,10,13,14}

There is also lingering concern that any association between abacavir and CVD could be an artifact of either “channeling bias” or the failure to adjust for potential confounders such as renal function or injection drug use.⁹ Indeed, patients at higher risk of CVD were more likely to receive abacavir^{1,15} (a “channeling bias”¹⁶ or “confounding by indication”¹⁷). The D:A:D did not adjust for time-varying risk factors such as blood lipid levels and blood pressure because, if they lie on a causal pathway between exposure to abacavir and CVD, adjusting for them could “adjust away” the effect of interest.¹⁸ This situation necessitates more complex methods of analysis; marginal structural modeling¹⁹ in particular has been recommended.^{18,20,21}

In most analyses, it is not known how the effect of exposure to a drug cumulates over time. Assuming a simple relationship between exposure and outcome can erode the power to detect a relationship and give a misleading picture of how best to minimize the risk of an adverse event.²² We assess the effect of exposure to abacavir on the risk of CVD events in the Swiss HIV Cohort Study (SHCS). First, we reproduce the D:A:D’s analysis using SHCS data; then, we consider the likely results had they used more complex statistical methods. We fit a new marginal structural model²³ to estimate the effect of abacavir as a flexible function of past exposures while accounting for risk factors that potentially lie on a causal pathway between exposure to abacavir and CVD.

METHODS

Patients

The SHCS is a prospective cohort with continuing enrollment of HIV-infected adults.²⁴ Since April 1, 2000, a cardiovascular risk assessment has been a part of follow-up visits scheduled every 6 months at 1 of 7 outpatient clinics or at the office of a collaborating physician. At each assessment, blood pressure, smoking status, weight, and body fat loss or gain are recorded, and a blood sample is taken to measure blood lipids. In this study, we include all patients with at least 1 cardiovascular risk assessment.

Outcome, Covariate, and Exposure Definitions

We consider a composite outcome to maximize the number of suitable disease events. As in the D:A:D study,¹ we define a CVD event as the first occurrence of either a myocardial infarction, an invasive cardiovascular procedure or a cardiovascular-related death. Each myocardial infarction or invasive cardiovascular procedure was documented in a checking chart²⁵; since 2005, each death has been documented using a cause of death form.^{26,27}

As in the D:A:D study, each patient’s follow-up is divided into consecutive 1-month periods in our analyses. To reproduce the D:A:D’s analysis, we adjust for the same covariates in our conventional multivariate models. Hence, these models have time-fixed covariates for demographic characteristics (age, sex, likely transmission through injection drug use, Caucasian ethnicity), calendar year, and CVD risk factors (family history of coronary heart disease, previous CVD event); and time-varying covariates for CVD risk factors (smoking status and body mass index, updated each follow-up visit) and cumulative exposure to 15 other antiretroviral drugs (with a separate covariate for each drug updated each month).

Time-varying covariates identified by the D:A:D as potentially on a causal pathway between exposure to abacavir and CVD are not included in our conventional multivariate models but are accounted for in our marginal structural Cox models. These covariates are represented by separate indicators for hypertension, dyslipidemia, and diabetes (and in a sensitivity analysis, an indicator for chronic kidney disease); indicators for 3 Framingham risk score categories²⁸; and continuous measures of CD4 cell count and log 10 HIV RNA (viral load).

When estimating the effect of abacavir as a flexible function of past exposures, exposure is represented by an indicator variable with value 1 if the patient was taking abacavir on the first day of the month. Other estimates of the effect of abacavir use exposure indicators and duration of exposure as at the first day of the month derived from the exact dates the patient started and stopped taking abacavir.

Statistical Analyses

We analyze time to the first CVD event using various forms of the Cox proportional hazard model. For each patient, follow-up begins at their first CVD risk assessment. A patient with no CVD event during follow-up is censored at a death unrelated to CVD, 6 months after their last CVD assessment if lost to follow-up or at the end of the study (30 September, 2012), whichever comes first. As in the D:A:D’s analyses, we assume that censoring is uninformative.

Conventional Modeling

We fit 3 conventional Cox models; all adjust for the same covariates, but the history of exposure to abacavir is represented in different ways. The first model reproduces an analysis reported by the D:A:D, with 2 time-varying exposure variables: one for the total duration of past use (cumulative use) and the other an indicator of any exposure within the

previous 6 months (recent use). The other 2 conventional models use exposure variables suggested by the results of our cumulative exposure modeling. These results suggest that current exposure to abacavir might be protective and that exposure during the past 6–36 months causes the greatest increase in the risk of a CVD event. Hence, the second model has 3 exposure variables: cumulative use as before, but with recent use partitioned into 2 indicators, use in the current month, and use in the previous 1 to 6 months. The third model has exposure to abacavir represented by 3 variables: current use, use in the previous 1 to 6 months, and the total duration of use over the past 7–36 months.

Marginal Structural Modeling

We also fit the models described above as marginal structural Cox models using stabilized inverse probability of treatment weights (see Section 1, Supplemental Digital Content, <http://links.lww.com/QAI/A680>). This process requires 8 different logistic regression models to estimate the probability that in a given month a patient either starts treatment with abacavir (if abacavir-naïve) or continues treatment with abacavir (if already exposed) given the most recent values of confounding variables. The process also allows relationships between confounding variables and treatment to change after February 2008 because prescribing behavior changed after the D:A:D's results were published.^{7,29}

Cumulative Exposure Modeling

We fit a new marginal structural model that estimates the effect of abacavir as a flexible function of past exposure while using the same inverse probability of treatment weights as above.²³ Exposure to abacavir is defined as a weighted sum of use in each past month, with (exposure) weights found by estimating a cubic spline for the relative importance of exposure at different times in the past. We assume that exposure more than 4 years ago would have no effect on the current risk of a CVD event. We consider 9 alternative weight functions (see Section 2, Supplementary Digital Content, <http://links.lww.com/QAI/A680>); these differ in their degree of flexibility and in whether weights are forced to take zero value at both the beginning and end of the 4-year interval, or just at the end of 4 years, or can take values other than zero at all times. A zero weight at the beginning of the 4-year interval implies that there is a lag between exposure and its effect on the current risk of an event. Having selected the best fitting weight function,³⁰ we estimate a hazard ratio (HR) comparing 2 different treatment strategies—always exposed to abacavir over the entire 4 years versus never exposed over this period.

Additional Analyses

We refit our weighted models with a time-varying indicator of chronic kidney disease added to the covariates used to calculate inverse probability of treatment weights (see Section 3, Supplemental Digital Content, <http://links.lww.com/QAI/A680>). This sensitivity analysis requires a truncated data set,

limited to follow-up after January 2002 when routine serum creatinine measurement began in the SHCS.³¹ We define chronic kidney disease as an estimated glomerular filtration rate (calculated using CKD-EPI equation³²) below 60 mL/min per 1.73 m².

In 2 unplanned sensitivity analyses, we refit models for abacavir after excluding patients infected with HIV through injection drug use and after excluding patients exposed to abacavir before their first cardiovascular risk assessment (see Section 4, Supplemental Digital Content, <http://links.lww.com/QAI/A680>). The second analysis avoids a bias that would arise if existing uses of abacavir were in a sense “survivors” at low risk of CVD,³³ and its population of abacavir-naïve patients corresponds to the “full population” used in a recent analysis by the NA-ACCORD.³⁴

We also perform a set of analyses for 2 other antiretroviral drugs from the same drug class: didanosine and tenofovir (see Sections 5 and 6, Supplemental Digital Content, <http://links.lww.com/QAI/A680>). The D:A:D collaboration found that recent exposure to didanosine was also associated with an increased risk of CVD events.¹ Didanosine and abacavir are both guanosine analogs and hence might plausibly have similar effects. However, tenofovir was not associated with an increased risk of CVD events, although subject to the same channeling biases as abacavir.³⁵

RESULTS

Patients

As at October 2012, 11,924 patients in the SHCS had at least 1 cardiovascular risk assessment, and 11,856 patients provided follow-up with all covariates available. These 11,856 patients have been followed for a total of 80,004 patient-years with a median follow-up of 6.6 years [interquartile range (IQR), 2.8–11.6]. Of these patients, 1549 were exposed to abacavir before assessments began, for a median duration of 0.7 years (IQR, 0.2–1.4). During follow-up, 4052 patients were exposed to abacavir, for a median duration of 3.4 years (IQR, 1.3–6.0), and of these, 2297 stopped taking abacavir during follow-up and 821 restarted again. During follow-up, 365 patients had a CVD event (3.0%); of these, 195 had been exposed to abacavir (53%), for a median duration of 3.4 years (IQR, 1.0–5.9). Half of the CVD events included a myocardial infarction (Table 1). Of the 11,491 patients without a CVD event, 4312 had been exposed to abacavir (38%), for a median duration of 3.3 years (IQR, 1.0–6.0). Patients who had a CVD event were older and more likely to be men, currently smoking, with a previous CVD event, or a family history of such events (Table 1). They were also more likely to have diabetes, chronic kidney disease, hypertension, dyslipidemia, or lipodystrophy and had higher Framingham risk scores than those without an event.

Conventional and Marginal Structural Modeling

In our first conventional model (Table 2), the risk of a CVD event increased with recent exposure to abacavir [HR =

TABLE 1. Characteristics of Patients at the Time of Their First CVD Event or If No Such Event, at Their Last Follow-up Visit—Median or Proportion

Characteristic	Patients With a CVD Event				Patients Without a CVD Event
	All	Exposed to Antiretroviral Therapy*			
		Exposed to Abacavir	Exposed to Didanosine	Exposed to Tenofovir	
General					
Number of patients	365	195	151	148	11,491
Male	0.83	0.83	0.81	0.83	0.70
Age, yrs	45	44	46	44	35
CD4 cell count, cells/μL	470	500	460	460	510
Suppressed viral load†	0.76	0.80	0.75	0.82	0.76
Body mass index >26, kg/m ²	0.25	0.23	0.22	0.26	0.26
Current smoker	0.61	0.58	0.59	0.61	0.47
Ex-smoker	0.21	0.22	0.22	0.25	0.21
Infected through injection drug use	0.22	0.22	0.24	0.26	0.19
CVD					
Previous event‡	0.14	0.12	0.13	0.12	0.01
Family history§	0.19	0.16	0.20	0.18	0.11
Diabetes mellitus	0.15	0.15	0.15	0.17	0.06
Chronic kidney disease¶	0.21	0.17	0.21	0.11	0.09
Hypertension					
Use of antihypertensive medication	0.43	0.43	0.36	0.45	0.18
Arterial hypertension#	0.59	0.61	0.54	0.64	0.34
Lipid levels					
Total cholesterol, mmol/L	5.4	5.5	5.6	5.4	4.9
HDL cholesterol, mmol/L	1.1	1.1	1.1	1.1	1.2
Use of lipid-lowering medication	0.32	0.32	0.35	0.33	0.10
Dyslipidemia**	0.65	0.63	0.68	0.62	0.36
Lipodystrophy††	0.45	0.46	0.54	0.48	0.27
Framingham risk score‡‡					
Low (<10%)	0.40	0.41	0.42	0.40	0.76
Moderate (10%–20%)	0.45	0.43	0.42	0.47	0.21
High (>20%)	0.15	0.17	0.15	0.14	0.03
CVD event§§					
Myocardial infarction	0.51	0.56	0.57	0.47	NA
Invasive cardiovascular procedure	0.72	0.72	0.72	0.76	NA
Cardiovascular death	0.12	0.10	0.14	0.08	NA

*Patients could be exposed to none of these 3 drugs or to 1 or more.

†HIV RNA undetectable or below 50 copies per milliliter.

‡CVD event before the patients first cardiovascular risk assessment.

§Myocardial infarction or stroke before the age of 50 in any first degree relative.

||Clinical diagnosis, or casual plasma glucose >11.1 mmol/L, or on antidiabetic medication or insulin.

¶Estimated glomerular filtration rate (calculated using CKD-EPI equation³²) <60 mL/min per 1.73 m².

#Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or on antihypertensive medication.

**Total cholesterol >6.2 mmol/L, high-density lipoprotein (HDL) cholesterol <0.9 mmol/L, or on lipid-lowering medication.

††Patient and clinician report either body fat loss or body fat gain.

‡‡Estimated risk of CVD in the next 10 years.

§§More than 1 event can occur during the same month.

|||Coronary angioplasty/stenting, coronary artery by-pass grafting, carotid endarterectomy, procedures on other arteries.

NA, not applicable.

1.50; 95% confidence interval (CI): 1.12 to 2.00] with weaker evidence of an increase with greater cumulative exposure (HR = 1.04; 95% CI: 0.99 to 1.10, per year). These estimates are close to the equivalent estimates reported by the D:A:D (HR = 1.63; 95% CI: 1.30 to 2.04, for recent exposure and HR = 1.03; 95% CI: 0.96 to 1.10, per year for cumulative exposure¹).

The other 2 conventional models use exposure variables suggested by the results of our cumulative exposure modeling

(Table 2, footnotes). The first of these 2 models suggests that recent exposure in the past zero to 6 months can be partitioned into current exposure and recent exposure in the previous 1 to 6 months. In this second model, current exposure has a protective effect (HR = 0.36; 95% CI: 0.23 to 0.55), whereas recent exposure increases the risk of a CVD event (HR = 3.69; 95% CI: 2.36 to 5.75) such that the mixing of current and recent exposure in the first model understates

TABLE 2. Relative Risk of a CVD Event for Patients Exposed to Abacavir

Exposure Parameters	Conventional Model*		Marginal Structural Model†	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Model 1‡				
Cumulative exposure (per year)	1.04	0.99 to 1.10	1.04	0.97 to 1.10
Recent exposure within past 0–6 mo	1.50	1.12 to 2.00	1.63	1.14 to 2.32
Model 2§				
Cumulative exposure (per year)	1.05	1.00 to 1.10	1.05	0.98 to 1.11
Recent exposure within past 1–6 mo	3.69	2.36 to 5.75	4.61	2.59 to 8.23
Current exposure	0.36	0.23 to 0.55	0.28	0.15 to 0.50
Model 3				
Cumulative exposure within the past 7–36 mo (per year)	1.25	1.04 to 1.51	1.22	0.98 to 1.52
Recent exposure within past 1–6 mo	3.20	1.97 to 5.19	4.06	2.24 to 7.34
Current exposure	0.35	0.22 to 0.54	0.27	0.15 to 0.50

*Models adjusted for age, sex, likely transmission through injection drug use, Caucasian ethnicity, family history of coronary heart disease, previous CVD event, smoking status, body mass index, calendar year, and cumulative exposure to 15 other antiretroviral drugs.

†Models fit using inverse probability weights, with weights found using 8 different logistic regression models. The covariates in these models included those used in the conventional models plus indicators for hypertension, dyslipidemia, diabetes, Framingham risk score categories, and continuous measures of CD4 cell count and log 10 HIV RNA.

‡Model 1 reproduced an analysis reported by the D:A:D—their estimates were HR = 1.03, 95% CI: 0.96 to 1.10, per year for cumulative exposure and HR = 1.63, 95% CI: 1.30 to 2.04, for recent exposure.¹

§Model 2 was suggested by cumulative exposure modeling—weight functions where the effect of current exposure could have a weight other than zero had negative weights for the earliest months of the 4-year interval suggesting that current exposure had a protective effect.

||Model 3 was suggested by cumulative exposure modeling—the best fitting weight function (Fig. 1, left) suggested that cumulating exposure to abacavir over the past 6–36 months causes the greatest increase in the risk of a CVD event.

the risk posed by the latter. The third model suggests that cumulative exposure during the past 7 months to 3 years (HR = 1.25; 95% CI: 1.04 to 1.51, per year) does indeed increase the risk of a CVD event, as predicted by our cumulative exposure modeling. Refitting these 3 models as marginal structural models led to very similar estimates (Table 2).

Cumulative Exposure Modeling

Of the 9 exposure weight functions, the best fitting weight function had a single knot and weights of zero at both the beginning and end of the 4-year interval (Fig. 1, left). This function implies that exposure to abacavir did not immediately increase the current risk of a CVD event; rather this risk reflects cumulating exposure to abacavir over the past 6–36 months. Of note, weight functions where the effect of current exposure could have a weight other than zero had negative weights for the earliest months of the interval suggesting that current exposure might have a protective effect (see Section 2, Supplemental Digital Content, <http://links.lww.com/QAI/A680>). The total effect of always being exposed to abacavir, during the entire 4-year period, versus never being exposed was HR = 2.06, 95% CI: 1.43 to 2.98 (Fig. 1, right). Cumulative exposure modeling without inverse probability weights gave a similar estimate of this total effect (HR = 2.10; 95% CI: 1.58 to 2.78; Fig. 1, right).

Additional Analyses

Estimates of the effect of abacavir were not attenuated when an indicator for chronic kidney disease was added to the covariates used to calculate inverse probability of treatment weights. Estimates of the effect of abacavir were not attenuated

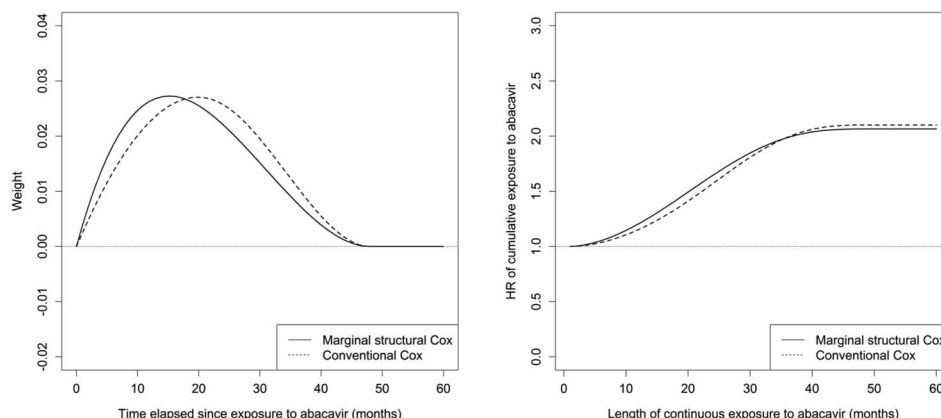
in unplanned analyses of patients not infected through injection drug use and of abacavir-naïve patients. Cumulative exposure modeling suggested exposure to didanosine had early harmful and then later protective effects (Fig. 2), whereas exposure to tenofovir had if anything a protective rather than a harmful effect (Fig. 3). Results for these additional analyses are summarized in Sections 3–6 of the Supplemental Digital Content (<http://links.lww.com/QAI/A680>).

DISCUSSION

Our results suggest that the risk of a CVD event increases as past exposure to abacavir cumulates, but only for a limited period. Exposure during the past 6–36 months causes the greatest increase in risk; both current exposure and exposure more than 3 years ago cause little additional increase in risk. Acute inflammation has been suggested as an explanation for the increase in CVD risk with exposure to abacavir because the risk seemed associated with recent and not past exposure.^{1,8} Our results suggest that other explanations should be sought because the increase in risk is not immediate and it cumulates so that past exposure within the last 3 years still influences current risk.

Note that the relative risks presented in Table 2 should not be interpreted too literally. The models in this table illustrate how different partitions of time—into current, recent, or cumulative use—can lead to different clinical conclusions. Our estimated weight function (Fig. 1, left) does not require this arbitrary partitioning and is therefore a more reliable basis for drawing clinical conclusions. Having estimated this weight function, a contrast between any 2 treatment histories can be generated, and we show one contrast of obvious interest—the

FIGURE 1. The effect of exposure to abacavir on the risk of CVD events: the estimated weight function (left) and the estimated total cumulative effect (as an HR) of always being treated with abacavir over the past 48 months versus never being treated with abacavir (right). Exposure more than 4 years ago was assumed to have no effect on current risk. Functions are shown for cumulative exposure modeling with both marginal structural (solid curve) and conventional (dashed curve) Cox models.^{23,36} Of the 9 alternative weight functions considered, the best fitting weight function had a single knot and (exposure) weights of zero at both the beginning and end of the 4-year interval.



effect of always being exposed to abacavir, over a 4-year period, versus never being exposed (Fig. 1, right).

With our data, we were able to reproduce estimates reported by the D:A:D despite the changes in prescribing behavior brought about by the publication of their results. Although the SHCS contributes data to the D:A:D, only 45% of our 365 events occurred before February 2007 and might therefore have been included in their original analysis. The results of our cumulative exposure modeling explain seemingly inconsistent results from earlier studies. If the harmful effects of exposure cumulate but only for a finite period, and yet patients are exposed to abacavir for much longer, cumulative exposure per year will seem weakly harmful at the best.^{13,35} Exposure to abacavir more than 6 months earlier may well seem harmful, although studies may lack the power to really confirm or rule out such an effect.^{1,37} Recent use should seem harmful, as it has in many studies,^{1,14,35,37} but may underestimate the short-term risk if current use is included in the definition of recent use because current use seems protective.¹³

An early protective effect could arise because abacavir, as part of an effective therapy, reduces viral replication, a risk factor for CVD events,^{38,39} or because of a “reverse causation bias”⁴⁰ if patients at high risk of a CVD event were taken off abacavir after only a short exposure but then went on to have such an event. Our modeling suggests that after the D:A:D’s results were published, patients with a previous CVD event or a high Framingham risk score were taken off abacavir (see Section 1, Supplemental Digital Content, <http://links.lww.com/QAI/A680>). But, of the 53 high-risk patients who stopped taking abacavir after February 2008, only 2 went on to have a CVD event and both had at least 5 years of exposure to abacavir.

This change in prescribing behavior was considered prudent.⁹ However, for patients who smoke, giving up smoking leads to a greater reduction in CVD risk than avoiding exposure to abacavir.^{6,41} For many patients, the increase in relative risk with exposure to abacavir will be acceptable, if other risk factors for CVD are absent,⁴² given the low rate of CVD events—4.6 per 1000 patient-years in

FIGURE 2. The effect of exposure to didanosine on the risk of CVD events: the estimated weight function (left) and the estimated total cumulative effect (as an HR) of always being treated with didanosine over the past 30 months versus never being treated with didanosine (right). Exposure more than 30 months ago was assumed to have no effect on current risk. Functions are shown for cumulative exposure modeling with both marginal structural (solid curve) and conventional (dashed curve) Cox models.^{23,36} Of the 9 alternative weight functions considered, the best fitting weight function had a single knot and (exposure) weights of zero at both the beginning and end of the 30-month interval.

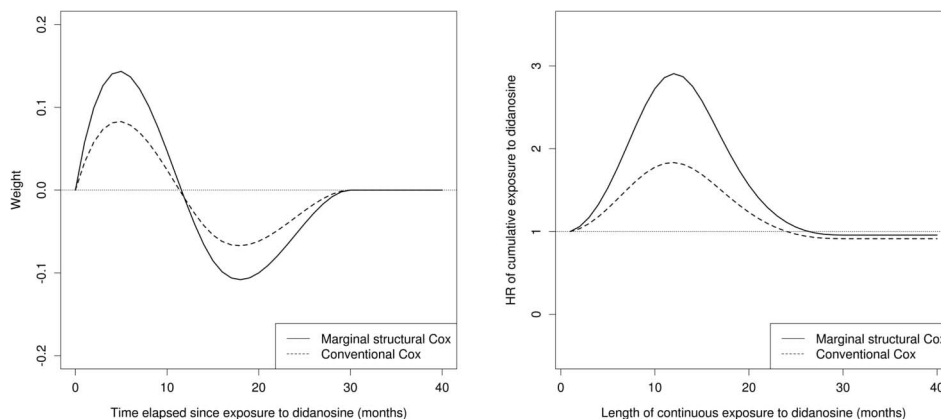
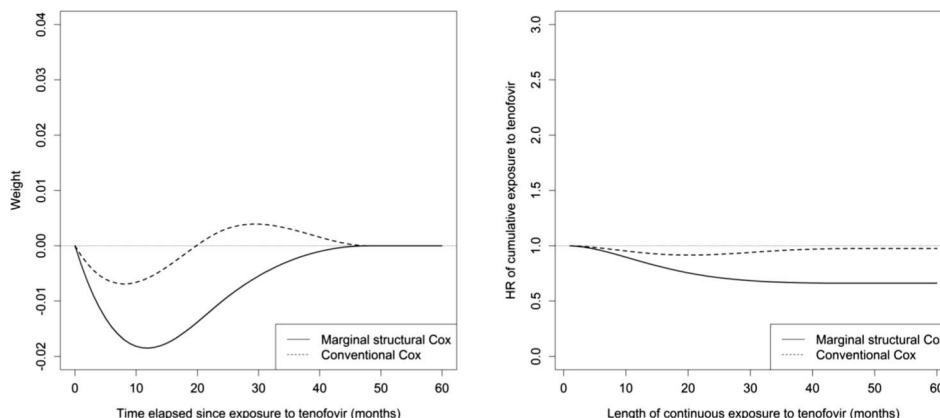


FIGURE 3. The effect of exposure to tenofovir on the risk of CVD events: the estimated weight function (left) and the estimated total cumulative effect (as an HR) of always being treated with tenofovir over the past 48 months versus never being treated with tenofovir (right). Exposure more than 4 years ago was assumed to have no effect on current risk. Functions are shown for cumulative exposure modeling with both marginal structural (solid curve) and conventional (dashed curve) Cox models.^{23,36} Of the 9 alternative weight functions considered, the best fitting weight function had a single knot and (exposure) weights of zero at both the beginning and end of the 4-year interval.



these data—and that alternatives such as tenofovir also have side effects.^{31,43} The question of whether—and how—abacavir increases the risk of CVD is still important. The recently approved coformulation of dolutegravir, a new integrase inhibitor, with abacavir and lamivudine provides a 1 pill once a day regimen once a day regimen that is likely to prove popular with patients.^{44,45} Integrase inhibitors are well-tolerated antiretrovirals because they do not interfere with normal cellular processes⁴⁶ and are therefore considered suitable for patients at risk of CVD.⁴⁷

Strengths of this study include that this is an analysis of data from a single cohort. This avoids the additional variation that arises when contributing cohorts in a multicohort collaboration use different methods to collect and measure data. Our CIs for estimates of effect sizes are of a similar width to those reported in the D:A:D's original study,¹ yet in our data, we have only half the number of CVD events (365 versus 693 events). We use modeling that does not require strong assumptions about the relationship between exposure and outcome. As a consequence, in our results, we see a relationship between exposure to abacavir and the risk of CVD events that is both plausible—in that risk lags exposure and does not cumulate indefinitely—and explains seemingly inconsistent results from earlier studies. Finally, unlike other observational studies, our analyses also account for covariates potentially on a causal pathway between exposure to abacavir and CVD; this reduces the residual confounding that would otherwise arise when those exposed to abacavir are at greater risk of CVD than the unexposed.¹⁸ Note that estimates in Table 2 with and without marginal structural modeling are similar, vindicating those who maintained that such modeling would not have altered the conclusions of their analyses.^{1,29,35} However, marginal structural modeling was important in our analysis of tenofovir (Fig. 3).

We note the following study limitations. As in the D:A:D study,¹ not all patients were abacavir-naïve at the start of follow-up, with 13% of patients pre-exposed. Those pre-exposed to abacavir had a higher prevalence of dyslipidemia and of moderate or high Framingham risk scores (data not shown), but our modeling of continued use of abacavir took such factors

into account. A causal interpretation of our results is only possible if there is no unmeasured confounding.¹⁹ We did not adjust for time-dependent injection drug use because routine recording of this only began in July 2008. Note, however, that sensitivity analyses of abacavir-naïve patients and of patients not infected through injection drug use gave similar results to the main analysis. We did not have sufficient events to warrant cumulative exposure modeling of the risk of myocardial infarction alone (Table 1).

The implication of these results is that a rapidly acting mechanism, such as acute inflammation,^{1,8} may not be responsible for the increased risk of CVD with exposure to abacavir. A possible early protective effect and a later cumulative harmful effect suggest more gradual processes. One possibility for a cumulative harmful effect is mitochondrial toxicity,⁴⁸ as abacavir may interact with cytidine analogs lamivudine and emtricitabine.⁴⁹ The heart, with its high metabolic demand, is rich in mitochondria and is susceptible to mitochondrial damage, especially as it ages.⁵⁰ Several mechanisms could be involved: equivalent modeling of the risk of CVD with exposure to didanosine suggests that the 2 drugs may affect CVD in different ways. Our results for didanosine suggest an unexpected dual effect—a rapid early harmful effect followed by a later protective effect (Fig. 2). This might explain why other studies show that recent exposure to didanosine is harmful but that cumulative exposure has no net effect^{1,35} or even a protective effect.³⁷ In the updated D:A:D analysis, plots showing the rate of myocardial infarction with cumulative exposure are consistent with what we report here—with abacavir, the rate increases and then levels off after 2 to 3 years of exposure; with didanosine, the rate seems to peak after about 1 to 2 years of exposure and may then decline.³⁵

Our results suggest a number of directions for future research. First, one could reconsider more gradual processes that might give rise to an increasing risk of CVD with cumulating exposure to abacavir. Second, one could look for evidence of a protective effect with current exposure to abacavir in data collected before the D:A:D's results prompted clinicians to take high risk patients off abacavir. Third,

one could consider whether the harmful effects of abacavir and didanosine might involve substantially different processes. Although our analyses suggest that exposure to abacavir increases the risk of CVD, they also suggest that acute processes are unlikely to be the cause.

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